B4

4. (Amended) The derivative according to Claim 3, wherein at least one of the amino acids serine, threonine or cysteine of the cyclosporin is replaced by the amino acid of formula I.

B5

6. (Amended) The derivative according to Claim 2, wherein it is derived from a cyclosporin in which the peptide chain contains at least one amino acid, chosen from serine, threonine and cysteine, in D or L configuration.

REMARKS

Favorable reconsideration and allowance of this application are respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made.**"

Claims 1-4 and 6 are pending in the application. The claims have been amended to recast them in more traditional format and to address the Section 112 matters set forth in the Office Action. The amended claims are supported by the original specification. In addition, the specification has been amended as requested on page 2 of the Official Action.

Claims 1-4 have attracted a Section 112, second paragraph, rejection. These claims have been recast in more traditional format and also address the Section 112 points. The amended claims are believed allowable.

Claims 1-3 and 6 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by the Wohr article (J. Am. Chem. Soc. 118, 9218, 1996). Applicants traverse this rejection based upon the following remarks and the attached evidence.

The claimed invention, including the invention of claim 4 that has not been rejected under 35 U.S.C. §102(b), is not disclosed by the Wohr article. All of the claims require "a cyclosporin derivative." The Wohr article does not disclose this feature of the claimed invention or other features. The Wohr article merely discloses peptides. As demonstrated below and supported by the attached exhibits, the claimed cyclosporin derivatives are different than regular peptides. Consequently, the Wohr article does not anticipate the inventions set forth in claims 1-4 and 6.

More specifically, the Wohr article merely describes a series of ***dipeptides*** containing the so-called "pseudo-proline" unit, used as a building block. Furthermore, Wohr merely discusses that such a building block offers a convenient temporary protection technique for Ser, Thr, or Cys, combined with several attractive features useful for the design and the synthesis of ***peptides*** (see, in particular, page 9223, right column, second paragraph). Among these features, this building block acts in solubilizing hydrophobic_protected segments and in preventing self-association of peptide fragments in convergent strategies or in chemoselective liqation approaches (see page 9223, middle of right column).

At most, the Wohr article shows that a pseudo-proline unit is a promising chemical tool in ***peptide*** synthesis. In this regard, in order to demonstrate all the properties of this chemical tool, the dipeptides containing a pseudo-proline unit have been incorporated into the synthesis of the following very specific peptides: "Switch peptide 8" (see page 9221, middle of right column), "Transmembrane peptide 9" (see page 9222, middle of left column), and Sarafotoxin-S6b (see page 9222, last paragraph in right column).

It is significant to note that the Wohr article does not provide any information suggesting a possible use of the pseudo-proline units to modulate the biological properties of these three

described peptides. And, even more importantly, the Wohr article does not provide any information suggesting a possible use of the pseudo-proline units as a chemical tool in order to synthesize cyclosporins. As a result, the Wohr article does not anticipate the claimed invention.

Moreover, without the improper hindsight use of the subject application, a person skilled in the art, when reading the Wohr article, is not inclined to use a pseudo-proline unit (described in the article merely as a "temporary" protective group) for the preparation of cyclosporin derivatives in order to improve biological properties.

Finally, the Office Action seems to consider that cyclosporin cannot be differentiated from a regular peptide and that its core structure is no longer recognizable as such. This is incorrect. Although cyclosporins and regular peptides both comprise amino-acid sequences, there are two major differences well known by persons skilled in this art.

The first one resides in their respective biosyntheses. Regular peptides are synthesized by the ribosomal pathway, whereas cyclosporins are obtained by microorganism. See **Exhibit 1**, Turner, Microbiology Today, 2000, Vol. 27, 118-20. As a consequence, the second difference resides in their respective chemical structure. The microbial peptides cyclosporins are cyclic peptides composed of eleven amino-acids residues, most of them amino-acids residues being non-proteinoic amino-acids. These non-proteinoic amino-acids are characterized for instance by N-methylated amide bonds, D- configuration, and/or unusual side chains. For these reasons and others, it is incorrect to state or infer that cyclosporins cannot be differentiated from regular peptides and that their core structure is no longer recognizable.

In further support of the differences, the academic community recognizes that cyclosporins are not considered classic peptides. For example, when consulting well-known textbooks and journals dealing with peptides, more specifically with peptide chemistry, the

academic community recognizes that cyclosporins are not considered classic peptides. See Exhibit 2, which is an index of the recent book -- Synthetic peptides; A user's guide, Second Edition, Ed. Gregory A. Grant, Oxford University Press, 2002. The index of this well known peptide textbook makes no reference at all to cyclosporins.

For all of the foregoing reasons and in view of the attached evidence, applicants respectfully request the withdrawal of the Section 102 rejection against claims 1-3 and 6. Correctly stated, the Wohr article does not disclose the claimed cyclosporin derivatives.

In view of the above amendments and remarks, and as supported by the attached evidence, applicants submit that all pending claims are in condition for allowance and earnestly solicit a notice to that effect. If the examiner has any questions, the undersigned may be contacted at 703-816-4009.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please insert the following beginning at page 2, line 6:

-- **BRIEF DESCRIPTION OF THE DRAWINGS**

- Fig. 1 shows the synthetic scheme for the synthesis of a cyclosporin derivative;
- Fig. 2 shows the synthetic scheme for synthesis of an intermediate in the preparation of the derivative of Fig. 1;
- Fig. 3 shows HPLC chromatograms over a period of time in a hydrolysis test of a cyclosporin derivative;
- Fig. 4 is a curve showing the variation with time of the concentration of the products in the same hydrolysis test; and
- Fig. 5 is a curve showing the kinetics of inhibition, by a cyclosporin derivative, of cis-trans isomerase activity in Cyclophilin A from calf thymus.

DETAILED DESCRIPTION OF THE INVENTION --

Please replace the paragraph beginning at page 4, line 17, with the following rewritten paragraph:

-- The properties of the cyclosporin derivatives of the present invention, the advantages offered by them, and the detailed method of preparation of these derivatives will be illustrated using the specific examples below, and with the help of the [drawing, in which] drawings. --

Page 4, please delete lines 22-32:

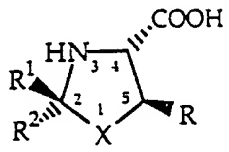
- [Fig. 1 shows the synthetic scheme for the synthesis of a cyclosporin derivative;
- Fig. 2 shows the synthetic scheme for synthesis of an intermediate in the preparation of the derivative of Fig. 1;
- Fig. 3 shows HPLC chromatograms over a period of time in a hydrolysis test of a cyclosporin derivative;
- Fig. 4 is a curve showing the variation with time of the concentration of the products in the same hydrolysis test; and].

Page 5, please delete lines 1-3:

- [Fig. 5 is a curve showing the kinetics of inhibition, by a cyclosporin derivative, of cis-trans isomerase activity in Cyclophilin A from calf thymus.]

IN THE CLAIMS

1. (Amended) A cyclosporin derivative in which the peptide chain comprises at least one residue of a non-natural amino acid of [general] formula I:



(I)

in which

X denotes an oxygen or a sulfur;

R denotes a hydrogen, or an alkyl group having between 1 and 6 carbon atoms;

R_1 and R_2 denote, independently of each other, a hydrogen, an alkyl group, having between 1 and 6 carbons, which may be straight-chain or branched-chain, substituted or non-substituted, an alkylene group having between 1 and 6 carbon atoms, a substituted or non-substituted aryl group, a substituted or non-substituted heteroaryl group, a residue of a water-soluble polymer, possibly bound to a spacer group.

2. (Amended) The derivative according to Claim 1, wherein [characterized in that,] in the amino acid of [general] formula I, R denotes a hydrogen or a methyl group.

3. (Twice Amended) The derivative according to Claim 1, wherein [characterized in that] it is derived from a cyclosporin in which the peptide chain contains at least one amino acid, chosen from serine, threonine and [Sistine] cysteine, in [d] D or [l] L configuration.

4. (Amended) The derivative according to Claim 3, wherein [characterized in that] at least one of the amino acids serine, threonine or [Sistine] cysteine of the [basic] cyclosporin is replaced by the amino acid of [general] formula I.

6. (Amended) The derivative according to Claim 2, wherein [characterized in that] it is derived from a cyclosporin in which the peptide chain contains at least one amino acid, chosen from serine, threonine and [Sistine] cysteine, in [d] D or [l] L configuration.